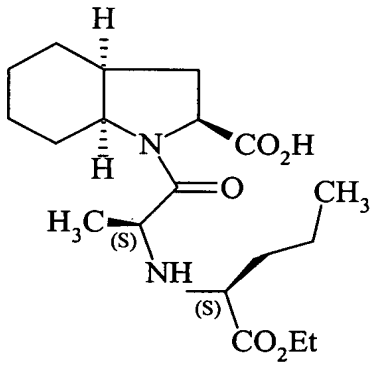
LISTING OF CLAIMS

1-11. (canceled)

12. (previously presented) A γ crystalline form of the compound of formula (I) :



. $tBuNH_2$ (I),

exhibiting essentially the following powder X-ray diffraction data, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray) :

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
6.298	14.02	630	39.8
7.480	11.81	380	24
8.700	10.16	1584	100
9.276	9.53	318	20.1
10.564	8.37	526	33.2
11.801	7.49	54	3.4
12.699	6.96	86	5.4
13.661	6.48	178	11.2
14.095	6.28	163	10.3
14.332	6.17	290	18.3
14.961	5.92	161	10.2
15.793	5.61	128	8.1
16.212	5.46	179	11.3
16.945	5.23	80	5.1

17.291	5.12	92	5.8
17.825	4.97	420	26.5
18.100	4.90	159	10
18.715	4.74	89	5.6
19.017	4.66	118	7.4
19.362	4.58	134	8.5
19.837	4.47	133	8.4
20.609	4.31	95	6
21.232	4.18	257	16.2
21.499	4.13	229	14.5
21.840	4.07	127	8
22.129	4.01	191	12.1
22.639	3.92	137	8.6
23.000	3.86	88	5.6
23.798	3.74	147	9.3
24.170	3.68	70	4.4
25.066	3.55	167	10.5
25.394	3.50	165	10.4
26.034	3.42	84	5.3
26.586	3.35	75	4.7
27.541	3.24	74	4.7
28.330	3.15	85	5.4
29.589	3.02	96	6.1

13. (previously presented) A process for the preparation of the γ crystalline form of the compound of claim 12, wherein a solution of perindopril tert-butylamine salt in chloroform is heated at reflux, the solution is then cooled to 0°C and the solid obtained is collected by filtration.

14. (previously presented) A process for the preparation of the γ crystalline form of the compound of claim 12, wherein a solution of perindopril tert-butylamine salt in ethyl acetate is heated at reflux, the solution is rapidly cooled, the solid thereby obtained is then collected by filtration, it is suspended in chloroform, the suspension is stirred at ambient temperature for 5 to 10 days, and the solid is then collected by filtration.

15. (previously presented) The process of claim 13, wherein the compound of formula (I) is obtained by a preparation process wherein

reduction of indole-2-carboxylic acid, or an alkyl ester thereof, followed by deprotection, if necessary, produces racemic indoline-2-carboxylic acid, from which the S isomer is isolated by adding the racemate to a solution of (+)-α-methylbenzylamine in a lower aliphatic alcohol, to obtain a precipitate of the salt formed by (S)-indoline-2-carboxylic acid with α-methylbenzylamine, which, after filtration, is dissolved in water and acidified, to produce (S)-indoline-2-carboxylic acid, which, after filtration and washing, is subjected to catalytic hydrogenation, under a hydrogen pressure of 10 to 150 bars, with heating to a temperature of 30 to 100 °C, wherein the catalyst is selected from rhodium, palladium, platinum and nickel, mixed with a support, followed by separation from the (2S, 3aR, 7aR) isomer by a single crystallization from a polar solvent selected from lower aliphatic alcohol, acetonitrile, ethyl acetate and dioxane, by itself or mixed with water, or mixed with each other and with water, to produce optically pure (2S, 3aS, 7aS)-perhydroindole-2-carboxylic acid which is then reacted with lower aliphatic or benzylic alcohol, in the presence of an acidic esterification catalyst, to produce the corresponding lower alkyl or benzyl ester;

(S)-L-norvaline is esterified with ethanol in the presence of an acid catalyst, to produce (S)-ethyl norvalinate, which is condensed under catalytic hydrogenation conditions, under a hydrogen pressure of 10 to 150 bars, wherein the catalyst is selected from rhodium, palladium, platinum and nickel mixed with a support, with pyruvic acid, to produce, after a single crystallization from a polar solvent selected from lower aliphatic alcohol, acetonitrile, ethyl acetate and dioxane, by itself or mixed with water, or mixed with each other and with water, cooling and filtration, optically pure N-[(S)-1-carbethoxybutyl]-(S)-alanine; and

the benzyl or lower alkyl ester of (2S, 3aS, 7aS)-perhydroindole-2-carboxylic acid is condensed with pure N-[(S)-1-carbethoxybutyl]-(S)-alanine in an alkaline medium in the presence of a catalyst for peptide synthesis, wherein the product obtained from the condensation is subjected

to deprotection of the carboxylic group of the heterocyclic ring, salification with tert-butylamine and crystallisation.

16. (previously presented) The process of claim 13, wherein the concentration of the compound of formula (I) in the chloroform is 150 to 300 g/litre.

17. (previously presented) The process of claim 14, wherein the compound of formula (I) is obtained by a preparation process wherein

reduction of indole-2-carboxylic acid, or an alkyl ester thereof, followed by deprotection, if necessary, produces racemic indoline-2-carboxylic acid, from which the S isomer is isolated by adding the racemate to a solution of (+)-α-methylbenzylamine in a lower aliphatic alcohol, to obtain a precipitate of the salt formed by (S)-indoline-2-carboxylic acid with α-methylbenzylamine, which, after filtration, is dissolved in water and acidified, to produce (S)-indoline-2-carboxylic acid, which, after filtration and washing, is subjected to catalytic hydrogenation, under a hydrogen pressure of 10 to 150 bars, with heating to a temperature of 30 to 100 °C, wherein the catalyst is selected from rhodium, palladium, platinum and nickel, mixed with a support, followed by separation from the (2S, 3aR, 7aR) isomer by a single crystallization from a polar solvent selected from lower aliphatic alcohol, acetonitrile, ethyl acetate and dioxane, by itself or mixed with water, or mixed with each other and with water, to produce optically pure (2S, 3aS, 7aS)-perhydroindole-2-carboxylic acid which is then reacted with lower aliphatic or benzylic alcohol, in the presence of an acidic esterification catalyst, to produce the corresponding lower alkyl or benzyl ester;

(S)-L-norvaline is esterified with ethanol in the presence of an acid catalyst, to produce (S)-ethyl norvalinate, which is condensed under catalytic hydrogenation conditions, under a hydrogen pressure of 10 to 150 bars, wherein the catalyst is selected from rhodium, palladium, platinum and nickel mixed with a support, with pyruvic acid, to produce, after a single

crystallization from a polar solvent selected from lower aliphatic alcohol, acetonitrile, ethyl acetate and dioxane, by itself or mixed with water, or mixed with each other and with water, cooling and filtration, optically pure N-[(S)-1-carbethoxybutyl]-(S)-alanine; and

the benzyl or lower alkyl ester of (2S, 3aS, 7aS)-perhydroindole-2-carboxylic acid is condensed with pure N-[(S)-1-carbethoxybutyl]-(S)-alanine in an alkaline medium in the presence of a catalyst for peptide synthesis, wherein the product obtained from the condensation is subjected to deprotection of the carboxylic group of the heterocyclic ring, salification with tert-butylamine and crystallisation.

18. (previously presented) The process according to claim 14, wherein the concentration of the compound of formula (I) in the ethyl acetate is 70 to 90 g/litre.

19. (canceled)

20. (currently amended) A solid pharmaceutical composition comprising, as active principle, an effective amount of the compound of claim 12, together with one or more pharmaceutically acceptable excipients or vehicles.

21. (previously presented) A method of treating a living animal body afflicted with a cardiovascular disease, comprising the step of administering to the living animal body an amount of the compound of claim 12 which is effective for alleviation of the condition.

22. (previously presented) The pharmaceutical composition of claim 20, which also comprises a diuretic.

23. (previously presented) The pharmaceutical composition of claim 22, wherein the diuretic is indapamide.

Polymorphs in Pharmaceutical Products

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Definition Of Polymorphs

- Polymorphs are different crystalline forms of the same pure substance in which molecules have different arrangements and/or different molecular conformation.

Definition Of Polymorphs (contd)

- Polymorphic solids have different unit cells.
- Display different physical properties such as unit packing, thermodynamic, spectroscopic, interfacial, and mechanical properties.

Physical Properties Differ Among Various Polymorphs

- Molar volume and density
- Refractive index
- Melting and sublimation temperatures
- Enthalpy (i.e., heat content)
- Solubility
- Vibration transitions (i.e., infrared absorption spectra and Raman spectra)

Physical Properties Differ Among Various Polymorphs (contd)

- Dissolution rate
- Stability
- Hardness
- Compatibility
- Handling, flow, and blending

Polymorphs

- An amorphous form is not a polymorph
- A clathrate or a hydrate can be a polymorph

Amorphous Forms

- Many pharmaceutical solids exist in amorphous forms and because of their distinctive properties are sometimes regarded as a polymorph.
- Unlike true polymorphs, an amorphous form is not a single type of crystal and not considered a polymorph.

Clathrate/Inclusion Compounds

- A chemical substance consisting of a lattice of one type of crystal structure trapping and containing a second type of molecule. Therefore, a clathrate is a material which is a weak composite, in which molecules of suitable size are captured in spaces which are left by the other compounds.
- Molecules of one substance are completely enclosed within the crystal structure of another.

Channel Hydrates Compound.xH_2O

- Hydrates in this class contain water in lattice channels, where the water molecules included lie next to other water molecules of adjoining unit cells along an axis of the lattice forming "channels" through the crystal.

Claiming A Polymorph

- Include name or structure of the chemical compound.
- Apply a "standard" convention to designate and name the polymorphic form and distinguish it from other polymorphic and pseudomorphic forms already in the art.
- Incorporate comparison and characterization data.

Structure of three compounds

- Cpd.HCl
- Cpd.H_2O
- Cpd.HCl.H_2O, a new compound

Polymorphs May Be Unobvious Over Prior Art Forms

- The specific crystal lattice(s) and number of lattices of a polymorph are not predictable.
- Even if one could predict that polymorphs exist, there is no general teaching or suggestion in the art that allows one to predict how to make a particular polymorph.
- No teaching or suggestion exists in the art to identify and to appreciate the properties and characteristics of a particular polymorph prior to it being identified.

Polymorphs May Be Unobvious Over Prior Art Forms (contd)

- A method of making the new polymorph was not known until its identification.
- The new crystalline form has different properties over the prior art compound.

Polymorphs May Be Unobvious Over Prior Art Forms (contd)

- It may not be obvious, and not possible to predict
  - How many different crystal forms can be prepared
  - How to prepare any, as yet unknown, crystal forms
  - The properties of any, as yet unknown, crystal forms

  Therefore, new crystal forms are potentially patentable entities

Include Available Polymorph Comparison and Characterization Data Such As:

XRPD

Single crystal x-ray

Infrared absorption

Raman spectroscopy

Solid state NMR

Morphology determination

Include All Available Polymorph Characterization Data Such As: (contd)

- Beyond having a diverse collection of characterization data, the data for a novel polymorph should be analyzed to demonstrate how it distinguishes over other disclosures including the compound per se, and more particularly, over other polymorphic forms.

Include all available polymorph characterization data such as (contd)

- Furthermore, characterization data that evidences unexpected or superior properties over properties of the compound per se, and other polymorphic forms, could make the prosecution easier.

QUESTIONS